REMARKS

Claims 41-46, 49-51, 56, 58, 59, 61, 63-73, 75, 77-82 and 87-96 are pending. Claims 1-40, 47, 48, 52-55, 57, 60, 62, 74, 76 and 83-86 are canceled. Claim 46 is withdrawn. Claim 59 has been amended for clarity purposes only rather than to narrow the scope of the claim. Support for this amendment can be found in the specification at least at page 10, lines 15-16, and page 35, line18 to page 37, line 12.

Information Disclosure Statement

The Examiner's attention is drawn to the fact that one reference (Verma et al.) in the Information Disclosure Statement re-submitted on January 26, 2007, has not yet been considered or is at least not yet initialed by the Examiner. Applicants respectfully request that the Examiner consider this document and indicate that it was considered by making appropriate notations on the corresponding Forms PTO-1449, to be returned to Applicants.

Claim Objection

37 C.F.R. 1.75(c) states that one or more claims may be presented in dependent form, referring back to and further limiting another claim or claims in the same application. There is nothing requiring that a claim, such as claim 51, depend from a previously numbered claim. 37 C.F.R. 1.75(c) only states that multiple dependent claims cannot serve as a basis for another multiple dependent claim. Furthermore, 37 C.F.R. 1.126 states that the Examiner will renumber the claims as appropriate once they are allowed. Applicants respectfully request withdrawal of this objection with the understanding that the Examiner will re-number and re-order the claims as necessary upon allowance.

35 U.S.C. § 112, Second Paragraph

Claims 41, 58 and 59 were rejected for allegedly being indefinite for the phrase "wherein the tissue specific promoter sequence is associated with probasin or a growth regulatory gene." Applicants respectfully point out that only claim 59 recites this phrase and thus claims 41 and 58 are clear and definite.

Claim 59 has been amended to clarify that the tissue-specific promoter sequence is a probasin promoter sequence or a growth regulatory gene promoter sequence. Support for this

amendment can be found in the specification at least at page 10, lines 15-16, and page 35, line18 to page 37, line 12. Claim 59, as amended, is clear and definite. Applicants respectfully request withdrawal of this rejection.

35 U.S.C. § 112, First Paragraph, Enablement

Claims 41-44, 49-51, 56, 58, 59, 61, 63-73, 75, 77-82 and 87-96 were rejected for allegedly lacking enablement for systemic administration of a retrovirus. The Examiner concedes that the application is enabled for local or topical administration of a retrovirus. The legal requirement is not to prove enablement for each and every species that may fall within the scope of the claim. Applicants again point out that as held by *Invitrogen Corp. v. Clontech Labs* and *Johns Hopkins Univ. v. CellPro, Inc.*, the enablement requirement is met if the description enables **any mode** of making and using the invention. *Invitrogen Corp. v. Clontech Labs.*, 429 F.3d 1052 (Fed. Cir. 2005); *Johns Hopkins Univ. v. CellPro, Inc.*, 152 F.3d 1342 (Fed. Cir. 1998). Thus, the standard of enablement has been met by the Applicants.

In contrast to the Examiner's characterization of Meng et al., Gene Therapy of Cancer, Chapter 1, pp. 3-20 (1999), page 6, column 1, Meng states that intravascular administration may be ***advantageous*** if the virus target is the liver. Therefore, Meng states that intravascular administration of viruses is useful in certain situations. Furthermore, the adequacy of a specification's description is not necessarily defeated by the need for some experimentation to determine the properties of a claimed product. *See Enzo Biochem, Inc. v. Gen-Probe Inc.*, 63 U.S.P.Q.2d 1609, 1614 (Fed. Cir. 2002). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *M.I.T. v. A.B. Fortia*, 774 F.2d 1104 (Fed. Cir. 1985). Those of skill in the art typically engage in systemic administration of viruses as evidenced by Meng. It is not necessary to "enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect." *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1338 (Fed. Cir. 2003). In addition, as set forth in MPEP § 2164.01(c), "the applicant need not demonstrate that the invention is completely safe." One of skill in the art would clearly be able to administer a

retrovirus systemically. Therefore, the claims are enabled and Applicants respectfully request withdrawal of this rejection.

35 U.S.C. § 103

Claims 41-45, 49-51, 56, 61, 66, 70, 71, 73, 75, 77-80, 87, 89 and 91 were rejected for allegedly being obvious based on Ram et al., Cancer Research 53:83-8 (1993) ("Ram") in view of Martuza, Nature Medicine 3:1323 (1997) ("Martuza") and U.S. Patent No. 5,585,096 ("the '096 patent").

The M.P.E.P. states that

> When applying 35 U.S.C. 103, the following tenets of patent law must be adhered to:
> (A) The claimed invention must be considered as a whole;
> (B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;
> (C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and
> (D) Reasonable expectation of success is the standard with which obviousness is determined.

(M.P.E.P. §2141 (II) citing *Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986)).

"To establish *prima facie* obviousness of a claimed invention, all the claim limitations *must* be taught or suggested by the prior art." *In re Royka*, 490 F.2d 981 (CCPA 1974). This basic criteria is not met by the cited references.

Ram describes a replication defective delivery vehicle for gene therapy. Martuza states that a replication competent adenovirus vector and a replication competent herpes simplex virus vector have been created. The '096 patent describes a replication competent herpes simplex virus vector.

Applicants respectfully point out that adenoviruses and herpesviruses are DNA viruses while retorviruses are RNA viruses. Furthermore, absent the disclosure provided by the present application, one of skill in the art would not have known how to modify a retrovirus in order to make it replication competent. As pointed out above, the claims are directed to retroviruses, which are RNA viruses, as described in the specification at least at page 15, lines 11-12.

Adenoviruses and herpesviruses are DNA viruses. Therefore, one of skill in the art would not have known how to make an RNA virus replication competent based on a disclosure of how to make a DNA virus replication competent as their genomes are completely different. Thus, the cited references do not disclose or suggest an RNA viral vector.

Ram, Martuza and the '096 patent, in combination, also fail to disclose or suggest, a method of treating a subject having a cell proliferative disorder comprising a) contacting the subject with a therapeutically effective amount of a retrovirus, comprising: a retroviral GAG protein; a retroviral POL protein; a retroviral envelope; an oncoretroviral polynucleotide sequence comprising Long-Terminal Repeat (LTR) sequences at the 5' and 3' ends of the retroviral genome; a heterologous nucleic acid sequence operably linked to a regulatory nucleic acid sequence, wherein the heterologous nucleic acid encodes a suicide gene; and cis-acting nucleic acid sequences involved in reverse transcription, packaging and integration in a target cell, in a pharmaceutically acceptable carrier; and b) contacting the subject with a prodrug which is activated by the expression of the suicide gene; wherein the cell proliferative disorder is a neoplastic disorder or associated with an overgrowth of connective tissue.

Specifically, Ram, Martuza and the '096 patent, in combination, fail to disclose or suggest a replication competent retrovirus comprising a retroviral GAG protein, a retroviral POL protein, a retroviral envelope, an oncoretroviral polynucleotide sequence comprising Long-Terminal Repeat (LTR) sequences at the 5' and 3' ends of the retroviral genome, a heterologous nucleic acid sequence operably linked to a regulatory nucleic acid sequence, wherein the heterologous nucleic acid encodes a suicide gene, and cis-acting nucleic acid sequences involved in reverse transcription, packaging and integration in a target cell. Therefore, the cited references do not describe or suggest each and every element of the claims as required for a claim to be rejected under 35 U.S.C. § 103. Therefore, the claims are not obvious based on Ram in view of Martuza and the '096 patent.

Applicants respectfully point out that it is the Examiner's burden to establish a *prima facie* case of obviousness. The U.S. Patent and Trademark Office has the burden under 35 U.S.C. § 103 to establish a *prima facie* case of obviousness. *In re Warner et al.*, 379 F.2d 1011

(C.C.P.A. 1967); *In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988). The Examiner has provided no evidence that the cited reference disclose or suggest all the claim elements as required for a claim to be rejected under 35 U.S.C. § 103. Therefore, the Examiner has failed to establish a *prima facie* case of obviousness.

In conclusion, the claims are not obvious based on Ram, Martuza and the '096 patent, and Applicants respectfully request withdrawal of this rejection.

Claims 41-45, 49-51, 56, 58, 59, 61, 66, 70, 71, 73, 75, 77-80 and 87-92 were rejected for allegedly being obvious over Ram in view of Martuza and the '096 patent and further in view of Kuryama et al., *Int. J. Cancer* 71:470-5 (1997) ("Kuryama") and Yan et al., *Prostate* 32:129-39 (1997) ("Yan"). As discussed above, Ram, Martuza and the'096 patent, in combination, fail to disclose or suggest each and every element of the claims. Kuryama and Yan do not make up for these deficiencies. Kuryama was cited for describing thymidine kinase (tk) under control of a liver-specific albumin promoter. Yan was cited for describing a probasin promoter. Therefore, Ram, Martuza, the '096 patent, Kuryama and Yan, in combination, do not disclose or suggest a replication competent retrovirus comprising a retroviral GAG protein, a retroviral POL protein, a retroviral envelope, an oncoretroviral polynucleotide sequence comprising Long-Terminal Repeat (LTR) sequences at the 5' and 3' ends of the retroviral genome, a heterologous nucleic acid sequence operably linked to a regulatory nucleic acid sequence, wherein the heterologous nucleic acid encodes a suicide gene, and cis-acting nucleic acid sequences involved in reverse transcription, packaging and integration in a target cell. The Examiner has provided no evidence that the cited reference disclose or suggest all the claim elements as required for a claim to be rejected under 35 U.S.C. § 103. Therefore, the Examiner has failed to establish a *prima facie* case of obviousness. The claims are not obvious based on Ram, Martuza, the '096 patent, Kuryama and Yan, and Applicants respectfully request withdrawal of this rejection.

Claims 41-45, 49-51, 56, 61, 63-70, 71-73, 75, 77-80, 81, 82, 87, 89-91, 93 and 95 were rejected for allegedly being obvious over Ram in view of Martuza and the '096 patent and further in view of Kasahara et al., *Science* 266:1373-6 (1994) ("Kasahara"). As discussed above, Ram, Martuza and the'096 patent, in combination, fail to disclose or suggest each and every

element of the claims. Kasahara does not make up for these deficiencies. Kasahara was cited for describing a replication incompetent retroviral vector encoding a chimeric envelope protein. Therefore, Ram, Martuza, the '096 patent and Kasahara , in combination, do not disclose or suggest a replication competent retrovirus comprising a retroviral GAG protein, a retroviral POL protein, a retroviral envelope, an oncoretroviral polynucleotide sequence comprising Long-Terminal Repeat (LTR) sequences at the 5' and 3' ends of the retroviral genome, a heterologous nucleic acid sequence operably linked to a regulatory nucleic acid sequence, wherein the heterologous nucleic acid encodes a suicide gene, and cis-acting nucleic acid sequences involved in reverse transcription, packaging and integration in a target cell. The Examiner has provided no evidence that the cited reference disclose or suggest all the claim elements as required for a claim to be rejected under 35 U.S.C. § 103. Therefore, the Examiner has failed to establish a *prima facie* case of obviousness. The claims are not obvious based on Ram, Martuza, the '096 patent and Kasahara, and Applicants respectfully request withdrawal of this rejection.

Claims 41-45, 49-51, 56, 61, 63-70, 71-73, 75, 77-80, 81, 82, 87, 89-91 and 93-96 were rejected for allegedly being obvious over Ram in view of Martuza and the '096 patent and further in view of Kasahara and Kuryama. As discussed above, Ram, Martuza and the'096 patent, in combination, fail to disclose or suggest each and every element of the claims, and Kasahara and Kuryama do not make up for these deficiencies. Ram, Martuza, the '096 patent, Kuryama and Kasahara , in combination, do not disclose or suggest a replication competent retrovirus comprising a retroviral GAG protein, a retroviral POL protein, a retroviral envelope, an oncoretroviral polynucleotide sequence comprising Long-Terminal Repeat (LTR) sequences at the 5' and 3' ends of the retroviral genome, a heterologous nucleic acid sequence operably linked to a regulatory nucleic acid sequence, wherein the heterologous nucleic acid encodes a suicide gene, and cis-acting nucleic acid sequences involved in reverse transcription, packaging and integration in a target cell. Therefore, the cited references do not describe or suggest each and every element of the claims as required for a claim to be rejected under 35 U.S.C. § 103. The Examiner has failed to establish a *prima facie* case of obviousness because the Examiner has provided no evidence that the cited reference disclose or suggest all the claim elements as

required for a claim to be rejected under 35 U.S.C. § 103. Therefore, the claims are not obvious over Ram, Martuza, the '096 patent, Kasahara and Kuryama.

Based on the claim amendments and comments provided herein, Applicants request allowance of the pending claims.

It is believed that no fee is due. However, please apply any charges or credits to deposit account 06-1050.

Respectfully submitted,

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